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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner : Celia C. Chang
Art Unit : 1625
Appellants : Marianne Langston, Hooshang Shahriari Zavareh
Serial No. : 09/928,139
Filed : August 10, 2001
Confirm. No. : 6929
For : Manufacture of Single Isomer Methylphenidate

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Honorable Commissioner of Patents
Attention: Board of Patent Appeals and Interferences
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY TO EXAMINER'S ANSWER TO SUPPLEMENTAL APPEAL BRIEF

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Doran R. Pace, Patent Attorney

As an initial matter, Appellants note that because of the numerous typographical and grammatical errors and omissions throughout the Examiner's Answer, it has been extremely difficult for Appellants to understand many of the points discussed by the Examiner. The following remarks are based on Appellants' good faith interpretation of what the Examiner was trying to convey in the Answer

I. RELATED APPEALS AND INTERFERENCES

The Examiner asserts that the Appeal Brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal. Appellants respectfully assert that the Brief does contain an appropriate statement. Page 1, Section II, of the Brief clearly states that "There are no related appeals or interferences." However, for purposes of clarity, Appellants hereby state that there are no other prior and pending appeals, interferences or judicial proceedings known to Appellants, the Appellants' legal representative, or the assignee which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

II. STATUS OF THE CLAIMS

Claims 1-8 are pending in application Serial No. 09/928,139 (hereinafter the '139 application or the subject application).

The final rejection of claim 1 for lack of enablement under 35 USC §112, first paragraph, as set forth in the final Office Action dated December 19, 2003 has not been reiterated in the September 29, 2004 non-final Office Action. Appellants assumed that the rejection had been withdrawn and did not specifically address it the Appeal Brief submitted February 28, 2005, except to state that if the Examiner intended that the rejection of claim 1 for lack of enablement under 35 USC §112, first paragraph, was maintained, then Appellants, in accordance with the provisions of MPEP 1208.02, incorporated by reference and in their entirety the arguments directed to the rejection as submitted in the Appeal Brief filed July 19, 2004.

In the Examiner's Answer, the Examiner indicated that the rejection of claim 1 for lack of enablement under 35 USC §112, first paragraph, was "inadvertent omitted" from the September 29, 2004 non-final Office Action. The Examiner has reinstated the arguments submitted in the Appeal Brief submitted on July 19, 2004. Appellants have addressed the Examiner's remarks set forth in the Examiner's Answer in the Argument section below.

In the Examiner's Answer, the Examiner also indicates that claim 1 is rejected under 35 USC §112, first paragraph, as lacking written description. This rejection was **not of record** in the Office Action dated February 14, 2003, nor in the Office Action dated December 22, 2003, nor in the Office Action dated September 29, 2004. However, the Examiner does not designate this rejection in the Examiner's Answer as a "new grounds of rejection." Therefore, Appellants respectfully assert that it is **improper** for the Examiner to include such a rejection in the Examiner's Answer unless the rejection is so designated as a new grounds of rejection in accordance with 37 CFR §41.39(b).

III. GROUPING OF CLAIMS

The Examiner asserts that Appellants Appeal Brief does not contain a statement that the grouping of claims does not stand or fall together and reasons in support thereof. Appellants respectfully assert that the Brief does contain such a statement and does contain reasons in support of the statement. The statements regarding the Grouping of Claims, as set forth at page 4, Section VII, of Appellants' Brief clearly states for each rejection that the claims rejected "do not stand or fall together" under the rejection. Reasons in support of the statements were set forth in the Arguments Section of the Brief. The Patent Office rules that pertain to the content of an Appeal Brief do not require that the reasons in support of the statement be included in the statement of the grouping of claims. Accordingly, Appellants respectfully assert that Appellants' explanation as to why the claims do not stand or fall together can be set forth in the Arguments Section of the Brief, as was done in the case of the Appeal Brief submitted February 28, 2005. See, for example, the first full paragraph at page 17 of the Appeal Brief submitted February 28, 2005, wherein it was stated that:

"Appellants also note that dependent claim 8 specifies that the racemization step of claim 1 comprises the use of a carboxylic acid and dependent claim 3 specifies that an achiral carboxylic acid is utilized. Appellants respectfully assert that the references cited under the §103 rejections do not teach or suggest complete

racemization of a single enantiomer of methylphenidate (or a molecule that has two chiral centers and is structurally analogous to methylphenidate) using a carboxylic acid as in claim 8 or an achiral carboxylic acid as in claim 3. In the absence of a teaching or suggestion in the art, and a reasonable expectation of success, to effect complete racemization of the molecule using the claimed acid, a *prima facie* case of obviousness is not established for the claims.”

Accordingly, Appellants respectfully assert that the statement as to the grouping of claims is satisfactory, that the Appeal Brief contains the reasons in support of the statements, and that the claims do not stand or fall together.

IV. ARGUMENT

A. Claim 1 is enabled and finds sufficient written description under 35 USC §112, first paragraph.

1. Statement of the rejection under 35 USC §112, first paragraph.

Claim 1 is rejected under 35 USC §112, first paragraph, as nonenabled and lacking sufficient written description.

The Examiner asserts in the Examiner’s Answer that the “limitation of producing all four isomer [sic] from the d- or l-threomer finds no antecedent basis or enablement.” The Examiner goes on to make various statements concerning the Great Britain priority applications. Appellants assert that these comments are mostly irrelevant to the issue of enablement and written description of Appellants’ invention. In addition, issues of “antecedent basis” are properly raised under 35 USC §112, second paragraph. Appellants respectfully assert that the subject application satisfies the requirements of 35 USC §112, first paragraph, regardless of the disclosure of the priority applications.

In regard to the enablement rejection, Appellants respectfully assert that the subject application (as well as Great Britain application No. 9618836.2) exemplifies the racemization of d-threo-methylphenidate into approximately equal amounts of all four possible stereoisomers. In other words, both chiral centers of the methylphenidate molecule have been epimerized equally. Support

for racemization of d-threo- methylphenidate can be found in the subject specification at page 4, lines 5-11. Thus, contrary to the Examiners assertion in the Answer, the subject specification discloses racemization of d-threo- methylphenidate to produce “all 4 stereoisomers of methylphenidate in roughly equal proportions.” (quotation from page 4, lines 10-11, of the specification). Appellants further assert that a person skilled in the art, having the benefit of the teachings of the subject application, would expect and predict that the same result would occur using l-threo-methylphenidate as the starting material, *i.e.*, that one would be able to racemize l-threo-methylphenidate into approximately equal amounts of all four possible stereo isomers. It is well settled that an applicant’s statements must be taken as true unless the Patent Office can cite specific reasons to doubt the truth of those statements. (*In re Marzocchi*, 169 USPQ 367 (CCPA 1971)). There is no reason or evidence presented by the Examiner to doubt Appellants statements. Thus, in the racemization step of the claimed method, either of the starting materials specified in the claim (*i.e.*, d-threo- or l-threo-methylphenidate) will give a mixture of all four isomers in approximately equal amounts.

B. Claims 1-8 are not *prima facie* obvious over any combination of:

i) Zeitlin *et al.* (U.S. Patent No. 5,733,756) or Armstrong *et al.* (1986) in view of Barry (1993), Miller (abstract 1980), or Miller (U.S. Patent No. 4,254,261); or

ii) Zeitlin *et al.* (U.S. Patent No. 5,733,756) or Armstrong *et al.* (1986) in view of Barry (1993), Miller (abstract 1980), or Miller (U.S. Patent No. 4,254,261) further in view of Harris (U.S. Patent No. 6,242,464).

1. Statement of the rejections under 35 USC §103(a).

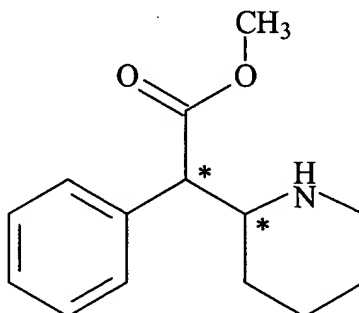
The Examiner maintains that claims 1-6 and 8 are unpatentable under 35 USC §103(a) as obvious over Zeitlin *et al.* (U.S. Patent No. 5,733,756) or Armstrong *et al.* (1986) in view of Barry (1993), Miller (abstract 1980), or Miller (U.S. Patent No. 4,254,261), and that claims 1-8 are unpatentable under 35 USC §103(a) as obvious over Zeitlin *et al.* (U.S. Patent No. 5,733,756) or Armstrong *et al.* (1986) in view of Barry (1993), Miller (abstract 1980), or Miller (U.S. Patent No. 4,254,261) further in view of Harris (U.S. Patent No. 6,242,464).

In the Examiner's Answer, the Examiner supplements these rejections with references that were not cited during prosecution of the application. These newly cited references are Gao *et al.*, Shimoju *et al.*, and Beausoleil *et al.* The Examiner does not cite these references as part of a new grounds of rejection, but rather cites these references in support of her statement that "racemization of dual [sic] chiral compounds gives *four isomer in thermodynamic mixture* is *prima facie* [sic] and is well known to one having ordinary skill." Appellants respectfully assert that the citation of new references constitutes a new grounds of rejection and, therefore, should have been raised during the several years of prosecution of the subject application, rather than at this late stage, so as to afford Appellants a complete and full opportunity to respond to the rejection and make amendments in light of the new references. During prosecution of the subject application, Appellants noted that the Examiner had not provided evidence (other than the references cited in the Office Actions) to support her position. Citation of the Gao *et al.*, Shimoju *et al.*, and Beausoleil *et al.* at this stage, *i.e.*, after several years of prosecution followed by a first Appeal and subsequent reopening of prosecution by the Examiner, followed by this Appeal, is unfair to Appellants. Accordingly, Appellants respectfully assert that the Gao *et al.*, Shimoju *et al.*, and Beausoleil *et al.* references are not of record in the subject application and should not be considered by the Board of Patent Appeals and Interferences in this Appeal.

However, Appellants will address the Examiner's Answer concerning the rejections under 35 USC §103(a). Appellants respectfully maintain that the claimed invention is not obvious over the cited references, including the Gao *et al.*, Shimoju *et al.*, and Beausoleil *et al.* references, regardless of whether the references are taken alone or in combination. As Appellants have previously pointed out, in order to establish a *prima facie* case of obviousness, the prior art must teach or suggest each

and every element and limitation of the claimed invention, and provide a reasonable expectation of success that the modification or combination will succeed. *In re Dow Chemical Co.*, 5 USPQ2d 1529 (Fed. Cir. 1988). A *prima facie* case of obviousness has not been established against claims 1-8 in the subject '139 application because none of the cited references, taken alone or in the combination asserted by the Examiner, teach or suggest Appellants' invention, nor do the cited references provide the required reasonable expectation of success.

Briefly, the claimed invention of the subject '139 application relies on racemization of a single enantiomer of methylphenidate. The product of such racemization is all four possible enantiomers of methylphenidate. Methylphenidate has the following structure, wherein each * represents a chiral center within the molecular structure:



As can be understood from the above structure, methylphenidate has two chiral centers within the molecule.

In regard to the original references cited, *i.e.*, the Zeitlin *et al.* (U.S. Patent No. 5,733,756), Armstrong *et al.* (1986), Barry (1993), Miller (abstract 1980), and Miller (U.S. Patent No. 4,254,261) references, Appellants maintain and reassert their arguments from the Appeal Brief submitted February 28, 2005. The Examiner acknowledged in the Office Action dated September 29, 2004 that the Zeitlin *et al.* and Armstrong *et al.* references do not teach a racemization step. Appellants respectfully assert that none of the other references cited in the rejections under 35 USC §103 teach

or suggest methods for racemizing single enantiomer methylphenidate or a structurally analogous molecule at both of the chiral centers in the molecule. This is evidenced by the lack of a reference being cited by the Patent Office specifically teaching the racemization of a single enantiomer of methylphenidate so as to produce all four possible stereoisomers, even after several years of prosecution of the subject application and the parent application. In making the rejections under 35 USC §103, no evidence or references have been presented or cited by the Patent Office which teach or suggest, **with the required reasonable expectation of success**, how an ordinarily skilled artisan might effect racemization of a single enantiomer of methylphenidate at both chiral centers of the molecule.

Appellants will briefly recap the failings of the teachings of the originally cited references. In regard to the Barry reference, Appellants respectfully assert that the amino acid esters (*e.g.*, leucine methyl ester) disclosed in the Barry reference have only one chiral center within the molecule itself.

Thus, any racemization that may be taught in the Barry reference is racemization of a molecule with a single chiral center, and not racemization of a single molecule with two chiral centers as provided in Appellants' claimed invention. Therefore, the amino acid esters taught in the Barry reference are not structurally analogous to methylphenidate and the racemization of such amino acid esters is not analogous to the racemization of methylphenidate.

The compound that is described in the Miller references (abstract (1980) and U.S. Patent No. 4,254,261), homopyrrolidone carboxylic acid (hereinafter referred to as HPCA), has only one chiral center. Thus, Appellants respectfully assert that the Miller references, contrary to the Examiner's assertion, are not analogous art.

In regard to the Harris patent (U.S. Patent No. 6,242,464), Appellants respectfully assert that the Harris patent is disqualified under 35 USC §103(c). The issue of disqualification of the Harris patent under 35 USC §103(c) was discussed in detail in section VIII, subsection D, of the Appeal Brief submitted February 28, 2005. Accordingly, Appellants respectfully assert that the statement submitted in the August 14, 2003 Amendment is sufficient to disqualify the Harris patent from being used in a rejection under 35 USC 103(a) against the subject '139 application. In the Office Action dated September 29, 2004, the Examiner did not acknowledge or address Appellants assertions regarding the disqualification of the Harris patent. Appellants note that the Examiner has not

explicitly withdrawn the rejection under 35 USC §103(a) that includes the Harris patent. In the Examiner's Answer, the Examiner states that "Although the examiner tried to keep track of the assignment, the continuous changing in assignment information made it very difficult. However, please note that the status of the Harris '464 reference is only applicable to claim 7. The 103(a) rejections over claims 1-6 and 8 which do not rely upon the Harris '464 reference are still relevant." Appellants are unable to determine from these statements whether the Examiner has or has not withdrawn the rejection that includes the Harris patent. Appellants respectfully assert that the Examiner should, on the record, unequivocally state whether she has accepted Appellants statements that the Harris patent is disqualified under 35 USC §103(c) and, therefore, the Harris patent cannot be used in a rejection of the claimed invention under 35 USC §103(a). The Examiner should then explicitly withdraw the rejection.

In regard to the newly cited Shimoju *et al.* reference, it teaches production of a mixture in which one (threo) pair of enantiomers is in a huge enantiomeric excess (99.5%) with respect to the opposite (erythro) pair of enantiomers(0.5%). Thus, the Shimoju *et al.* reference does not teach or suggest, with a reasonable expectation of success, a means for obtaining all four stereoisomers of methylphenidate in approximately equal proportions. The results obtained by Shimoju *et al.* are useless, for practical purposes, if the desired enantiomer was in the minor product. One cannot readily recover something which is hardly there. Appellants further note that for the molecule disclosed in the Shimoju *et al.* reference, the two chiral centers are both on the alkyl chain rather than the cyclic moiety. In contrast, methylphenidate has one chiral center on a carbon of the heterocyclic moiety and the other chiral center on the alkyl chain moiety. Thus, the chiral center for one of the carbons of methylphenidate is more sterically hindered than the carbons of the molecule in the Shimoju *et al.* reference.

The newly cited Gao *et al.* reference does not teach or suggest racemization of single enantiomer methylphenidate, or a molecule structurally analogous to methylphenidate, that results in production of all four stereoisomers. The statement in Gao *et al.* relied upon by the Examiner is simply a statement that the feasibility of racemization of an "unwanted" enantiomer to allow for recycling of that enantiomer impacts the economics of a particular resolution process. Appellants note the Gao *et al.* authors' use of the word "feasibility;" thus, the authors recognize that not all

molecules having chiral centers may be readily racemized from a single enantiomer starting material. Thus, the Gao *et al.* reference underscores Appellants' assertion as to the unpredictability, prior to Appellants' invention, of whether a single enantiomer of a molecule such as methylphenidate can be racemized to produce all four enantiomers in useful proportions. Simply put, one cannot reasonably predict, a priori, to what extent, if any, a single enantiomer can be racemized into all possible stereoisomers.

Similarly, the Beausoleil *et al.* reference does not teach a molecule that is structurally analogous to methylphenidate. Moreover, the reaction pointed to by the Examiner in the Beausoleil *et al.* reference only results in the production of diastereomers in a ratio of 3:1, rather than the approximately equal amounts produced by the Appellants' method.

Appellants maintain that it was not predictable that an enantiomer of methylphenidate could be racemized to produce all four enantiomers. Attached as Appendix C of the Appeal Brief submitted February 28, 2005 is a Declaration of Dr. Hooshang S. Zavareh Under 37 CFR 1.132. In his Declaration, Dr. Zavareh points out that racemization of an enantiomer of methylphenidate so that all four enantiomers are obtained requires abstraction of a proton. Dr. Zavareh states that it is, therefore, surprising that an acid, as is recited in the claimed method, could be used to racemize a single enantiomer of methylphenidate into all four possible enantiomers. The Examiner has not provided any arguments or evidence to rebut or question the statements or conclusions in Dr. Zavareh's Declaration.

In addition, Appellants also attached as Appendix D of the February 28 Appeal Brief an article by Dr. Mahavir Prashad entitled "Approaches to the Preparation of Enantiomerically Pure (2R,2'R)-(+)-*threo*-Methylphenidate Hydrochloride" (2001, *Adv. Synth. Catal.*, Vol. 343, No. 5, pp. 379-392). The article is a review article and concerns methods for producing enantiomerically pure methylphenidate. Appellants have reprinted below a portion of Dr. Prashad's article (from page 383, section 4):

A resolution process is more attractive and economical if the undesired enantiomer can be recycled via racemization. However, in the case of methylphenidate, such a racemization is challenging because there are two stereogenic centers which have to be epimerized. A method to affect the racemization at both stereogenic centers has been demonstrated by refluxing a solution of (2R,2'R)-*threo*-methylphenidate (1)

with propionic acid in toluene to afford a mixture of four stereoisomers in roughly equal proportions. (citing published International Application No. WO 97/28124) (emphasis added)

First, Dr. Prashad indicates that “racemization [of methylphenidate] is challenging” because there are two chiral centers in the molecule. This is precisely the point that Appellants have argued during prosecution of the ‘139 application racemization of a molecule of methylphenidate having two chiral centers so as to produce roughly equal amounts of all four possible stereoisomers is not predictable, conventional or obvious. It is the presence of two chiral centers (one of which is more sterically hindered than the other) in the methylphenidate molecule that, prior to Appellants’ invention, made complete racemization starting from a single enantiomer “challenging” and unpredictable.

Second, Dr. Prashad also references published International Application WO 97/28124 as the first publication to describe a successful means for the complete racemization of a single enantiomer of methylphenidate into all four stereoisomers. Dr. Prashad does not reference any other publications as teaching or suggesting a means for racemization of single enantiomer methylphenidate into all four possible enantiomers. Published application WO 97/28124 application, a copy of which is attached with this Appeal Brief as Appendix E, is the corresponding international filing of the subject ‘139 application. Appellants chose to file an international PCT application (international application No. PCT/GB97/00281, which was published as WO 97/28124) and a separate U.S. utility application (*i.e.*, application Serial No. 08/792,415 filed February 3, 1997, which is the parent application to the subject ‘139 application) under 35 USC §111 (rather than designating the U.S. in the international application and subsequently filing a national stage application under 35 USC §371). Appellants note that the subject ‘139 application and the WO 97/28124 application have identical inventorship, claim priority to the same British patent applications, and have the same disclosure in the specification. Thus, Dr. Prashad is, in essence, referencing the subject ‘139 application as teaching the first successful means for the complete racemization of a single enantiomer of methylphenidate into all four stereoisomers.

The Examiner has not rebutted or addressed the statements by Dr. Prashad. Accordingly, Dr. Zavareh's Declaration Under 37 CFR 1.132 and the published article by Dr. Prashad provide further evidence as to the nonobviousness of claims 1-8 of the '139 application.

In view of the above arguments and evidence presented herein, Appellants respectfully request reversal of all of the rejections set forth under 35 USC §103(a).

C. Claims 1-8 are not *prima facie* obvious over claim 1 of U.S. Patent No. 6,121,453 (Zavareh) in view of Miller (abstract (1980)), Barry (1993) or Miller (U.S. Patent No. 4,254,261) further in view of Harris (U.S. Patent No. 6,242,464).

1. Statement of the rejection based on "obviousness-type" double patenting.

Claims 1-8 are unpatentable under the judicially created doctrine of obviousness-type double patenting over claim 1 of U.S. Patent No. 6,121,453 (Zavareh) in view of Miller (abstract (1980)), Barry (1993) or Miller (U.S. Patent No. 4,254,261) further in view of Harris (U.S. Patent No. 6,242,464).

Appellants incorporate herein their remarks in their entirety regarding the Zavareh patent as set forth in the February 28, 2005 Appeal Brief and assert that the claimed invention is not obvious over the cited reference.

In regard to the secondary references cited under the obviousness-type double patenting rejection, including the newly cited Gao *et al.*, Shimoju *et al.* Beausoleil *et al.* references, Appellants respectfully reassert their comments from the February 28, 2005 Appeal Brief and their comments presented herein addressing the same secondary references cited in the rejections under 35 USC §103(a) and hereby incorporate those remarks by reference in their entirety. As noted in regard to the rejections under 35 USC §103(a), none of the secondary references teach or suggest, with the required reasonable expectation of success, means for racemization of a single enantiomer of methylphenidate, or any other single molecule analogous in structure to methylphenidate and having two chiral centers, so as to produce all four individual enantiomers.

Appellants respectfully request reversal of the rejection of claims 1-8 as unpatentable for obviousness-type double patenting over claim 1 of U.S. Patent No. 6,121,453 (Zavareh) in view of

Miller (abstract (1980)), Barry (1993) or Miller (U.S. Patent No. 4,254,261) further in view of Harris (U.S. Patent No. 6,242,464)

In view of the foregoing, Appellants urge that the Board reverse the 35 USC §112, first paragraph, rejection, the 35 USC §103(a) obviousness rejections and the obviousness type double patenting rejection of record in the subject '139 application and that this application be passed to issuance.

Respectfully submitted,



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